Down-scaling of a fluidised bed agglomeration process

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1 An introduction to fluid bed agglomeration

This chapter contains a short general overview on granulation and on agglomeration in a fluidised bed in particular.

1.1 Introduction

Agglomeration is the binding of fine powder particles to form a large porous structure. It is often used in the powder processing industries. Agglomeration of small particles improves handling properties of the powder such as flowability and reduces dust formation. This is important when the material is toxic or if there is a risk for dust explosion. Other improvements of the agglomerated powder are a higher dissolution rate by reducing lump formation or flotation of the powder. A higher bulk density achieved by agglomeration results in lower transport costs and a better compactability for a following tabletting process.
Granulation can be accomplished in various ways: dry roller compaction, spray drying, wet agglomeration or melt granulation. Wet agglomeration is widely used to make porous granules for various applications in the pharmacy, food and detergents industry. A liquid is sprayed upon a moving bed of particles where the liquid binds the particles by capillary forces. A binder compound can be dissolved into the spraying liquid, or premixed in the bed of powder particles. Due to evaporation of the binder solvent, liquid bridges will solidify at the contact points between particles. The binder liquid is mostly water with some polymer added to it, but other solvents are also used.

Wet agglomeration can be performed in fluid beds, rotating drums or high-shear mixers. As a result of rupture forces in the granulation apparatus, bonds between particles may be broken. In that case, the growth rate of granules depends on the rate of bond formation and bond rupture. Because the forces are very dependent on the apparatus used, this apparatus affects both the rate and the mechanisms of granule growth, as well the physical properties of the granule. For instance, the wet granulation process performed in high-shear equipment will produce denser granules than in low-shear equipment. This is due to densification of the material because of the higher forces applied on the agglomerates [1]. The choice of granulation equipment should therefore depend on the desired product properties.

Although fluid bed agglomeration is widely used in industry, engineers encounter problems when formulating a good (new) granular product. One of the reasons for these problems is that the granulation process is not only determined by the process application, but also depends on the properties of the materials used. Therefore, mechanisms involving granule growth are determined by both the apparatus and material used, and their relation to each other. It is therefore necessary to consider material properties which determine the granule growth in relation to the process.

Uniformity between batches is a necessity, especially in the pharmaceutical industry. The quality of the granular products should be well defined and constant i.e. independent of their lot number. Unfortunately, these requirements can not always be fulfilled. Sometimes the quality of the product can be improved by size classification, for instance by sieving. The disadvantage of this is a large recycle flow, which requires reprocessing of rejected product and increasing the size of the apparatus. Therefore, it would be most desirable to achieve a well-defined product without using classification methods, i.e. 'right first time'. Good process control might be achieved with a good fundamental knowledge of the mechanisms involved in agglomeration. Unfortunately, granulation is still considered an art rather than a science [1].

Over the past decades, there has been an increase of the potency of new drugs, resulting in very low levels of active components in tablets and capsules entering the market. Examples of these type of drugs are estrogens, corticosteroids, anti-hypertensives (such as cilazapril or moxonidine) and anti-psychotics (risperidon) [2]. We expect this trend of increasing drug potency and resulting low dosage formulation to continue with the influence of 'the new biotechnology' [3], for example with the use of small peptides (or peptides mimics). The granules required for producing these tablets consist largely of excipients, such as starch, lactose, microcrystalline cellulose or salts, and will contain only a small fraction of the active drug component. The pharmaceutical entity can be added premixed with the excipients before the agglomeration, suspended in the binder liquid during agglomeration, or added to the granules after the agglomeration. Such low dosage applications bear an increased risk of an insufficient uniformity of the active component [4].

More recently the Barr decision (or judge Wolin decision) [The US vs. Barr laboratories court ruling 812, F. supp. 485, D.N.J. 1993] again stressed the requirement of the homogeneity of powder blends. This gave rise to an enormous discussion within the pharmaceutical field on the predictability of blend homogeneity and numerous pitfalls in powder sampling [4-7].

The homogeneity of powder blends will, as the trend to an increase of drug potency develops, become an increasing challenge for industry. A major effort

should be made to improve both blend quality and validation methods to overcome future problems in achieving homogenous powder blends. The subject of this thesis is improving the fundamental knowledge about the agglomeration process in the fluid bed, which is necessary to achieve better blend quality.

1.2 Fluidised bed agglomeration

Control of the fluidised bed agglomeration process is difficult. Wetting, drying and mixing of particles all occur simultaneously in the bed. The different processes affect each other and are therefore difficult to control independently. It is necessary to understand the mechanisms involved and their relation to each other. Some authors [1, 8, 9] made an extensive summary of the mechanisms which take place during fluid bed agglomeration or wet agglomeration.
Aulton and Banks [10] classified several factors which influence the granulation process into three categories: (a) equipment related, (b) process related and (c) product or formulation related. Below, the relevant factors are given with their effect on fluid bed agglomeration; they can be used as a rule of thumb for designing an agglomeration process.

Equipment related factors (a)

The equipment parameters which are mentioned in literature are: *the air distributor plate* [11-15], *granulator bowl geometry* [12], *nozzle type height and location* [13, 16-21] and *mechanical agitators or choppers* placed in the bed [22, 23].
The air distributor plate is responsible for the uniform distribution of fluidising air throughout the bed. The pressure drop over the distributor plate should be at least one-third of the pressure drop over the bed to ensure uniform fluidisation. Ormos et al. [13] found that the type and quality of the distributor plate had hardly any effect on granule properties such as mean granule size, size distribution or porosity. However, it was found by others [14, 15] that perforated plates and bubble caps (compared to porous plates) do minimise segregation due to an increased bubble size and a high local gas velocity. We assume that the fluidisation intensity can be an important factor, which decides whether the distributor plate is significant for the granulation process.
The granulator bowl geometry is preferably conical shaped, with a ratio of cross-sectional diameter of the bottom plate to the top equal to 1:2 to 1:2.5. The air velocity must drop from bottom to the top of the rim of the bowl by more than one half to avoid entrainment of the smaller particles and segregation of large granules [11].
Extensive research has been done to examine the effects of *nozzle type and location* in the bed. The nozzle is an important instrument to distribute the moisture on to the

fluidising particles. Preferably, twin-fluid nozzles with external mixing are used to spray droplets, because the droplet size can be varied independently from the liquid flow and the chance of clogging is reduced by the extended liquid insert. The nozzle can be placed above, or in the bed, spraying sideways, upwards or downwards. Some authors [19, 20] used twin-fluid nozzles with internal mixing. They could not avoid the caking of the nozzle. They placed the nozzle in the bed at the bottom and were able to avoid caking of the nozzle by spraying upwards, although wet quenching occurred at lower liquid feed rates compared to top spraying. A disadvantage of spraying in the bed is the enlarged attrition of granules due to the high air velocities near the nozzle [15].
In literature several applications of a fluidised bed with *mechanical agitators* are described [22, 23]. In principle, the agitator was placed in the bed to improve granulation, by improving the poor fluidisation of cohesive powders, such as channelling [22]. The agitators are also used to break up granules and thus establish an equilibrium between the growth rate of granules and the break-up rate, resulting in a narrow granule size distribution and higher granule density [23].

Process related factors (b)

Process related factors, which are used to control the fluid bed agglomeration process, are *fluidising airflow rate* [8, 20], *temperature (inlet air)* [10, 24, 25], *the (relative) humidity* [25-27] *and the nozzle operation* [16, 19, 28, 29].
The fluidising air should not have a velocity which is too high, because fine powder will be blown out of the bed. This may result in clogging the filters. A fluidisation velocity which is too low will result in defluidisation (wet quenching) of granules during agglomeration. It was found that an increased fluidisation velocity resulted in a smaller granule size due to increased evaporation and attrition [10, 24, 25]. In fact, the fluidisation velocity, temperature and humidity have a direct effect on the moisture capacity of the fluidising air [8], and through this on fluidisation behaviour and granule growth.
A high *inlet air temperature* results in smaller and denser granules than a low inlet temperature.
Several authors used the bed *humidity*, moisture content or the bed temperature as the control parameter for the process [25-27]. These control parameters are all related to the liquid concentration in the fluid bed. The liquid concentration determines the adhesion between the particles and thus the agglomeration. It was found that the relative humidity, which is related to the bed temperature and the moisture content of the granules, influences the granule size. A high relative humidity results in large granules, a low relative humidity result in smaller granules.
The nozzle is a very important instrument to control the granule size. The liquid flow rate of the nozzle should be balanced with the evaporation rate. A high liquid

flow will result in overwetting the bed. A low liquid flow rate or very small droplets may result in (partial) spray drying of the binder liquid. Several authors [27, 29, 30] found a linear relationship between the binder flow rate and the mean granule size. The moisture content of the bed should be monitored to prevent the overwetting (wet quenching) of the bed or spray drying of the binder.
The nozzle determines the droplet size distribution, the spray rate and spray pattern upon the spray surface. The nozzle can be characterised independently of the granulation process itself, which makes it a good tool to control the process.
In the late seventies Scheafer and Worts wrote a series of articles [16, 17, 25, 27, 31] describing important mechanisms which determine the granule growth process in a fluidised bed. One of the major conclusions from their work was the relationship between droplet size and granule size. This indicated that under certain conditions rupture of granules is of minor consequence, because the relation between droplet size and granule size is preserved during the process. In the early nineties, Waldie [28] did some supplementary experiments where he introduced large droplets (diameter of ~3 mm) in a fluidised bed, and found a relationship between droplet size and primary granule size. Although the granules were large, three to 5 mm, they were believed to be representative of the mechanisms involved. Again, it was concluded that the rupture of granules is of not significant, if the binder added to the spraying liquid results in enough strength between the particles. This result was to be expected, because a fluidised bed is a low-shear device. This is also illustrated by the high porosity of agglomerates made in the fluid bed (ε is 0.4 - 0.5) compared to high-shear devices (ε is 0.2 - 0.3). the densification of the granules by external forces within the fluid bed plays only a minor role. Little is known about the influence of the droplet size on the mechanism of growth. Pioneers such as Rumpf and Newitt [32-34] showed that capillary forces highly affect the strength of the wet agglomerate. Ennis [35, 36] proved that the contribution of viscous forces, which contribute to the strength, could not be neglected in a dynamic situation. The distribution of liquid in a granule was only studied in minor detail [28, 37]. Obviously, if the rupture forces are small compared to the agglomerate strength, these rupture forces will hardly affect the agglomerate growth process.

Product and formulation related factors (c)

Product and formulation related factors influence the agglomeration process largely. The *fluidising properties* of the staring material [27], *the wettability* of the particles [25, 38-40] in combination with the solvent, *binder type* [8, 17, 41] *and concentration* [27, 29, 31, 41] greatly affect the agglomeration. Due to the absence of shear in the fluid bed, the effect of the product properties such as wettability is expected to be larger than in a high-shear granulation device. The product and its formulation are determined beforehand. The manufacturing process then has to maintain the properties of the granules. In many situations, especially in the

pharmaceutical industry, little can be done to change the formulation. This is because the materials in the formulation are essential for the final product or changes are restricted by registration of the product. In pharmacy, an early formulation is important for registration purposes and clinical phase studies of medicine. The formulation made in the large-scale process should perform in the same manner as in the small-scale process. This is not always easy to achieve.

In general, *the fluidising properties* of the starting material are mostly poor. This is not surprising, as the improvement of flowability is one of the reasons for granulating [42, 43]. Tribo electrified powders or cohesive powders are therefore commonly used as starting product [27]. Some research has been done on agglomeration of glass beads [15, 20, 44-47] used as a model compound. These glass beads have a much higher density, are smooth, spherical and inert and behave quite differently compared with commonly used products in industry. They are expected to be more sensitive to shear forces in a fluidised bed [20]. Although glass beads have the advantage of being well defined and are therefore preferred for modelling, the translation of experimental results to common conditions should be done with caution.

The wettability [48-51] of the particles is important for the wet agglomeration process. Poor wettability results in smaller granules, and these materials need higher spray rates to promote a slight overwetting of the material. Addition of surfactants premixed to the powder or to the binder liquid improves wetting [10].

The binder type choice depends on properties which are required for agglomeration or for further processing such as tabletting. The choice can also depend on pharmaceutical compatibility [52-54]. Commonly used binders are polyvinylpyrolidone (PVP), (modified) starch, gelatine, acacia and hydrophilic cellulose derivatives such as carboxymethylcellulose and hydroxypropylcellulose. The strength of a granule depends on the binder amount and the binder type. The binder should preferably be sufficient to withstand the rupture forces encountered in the fluid bed. An increase of *binder concentration* was found to increase the granule size and reduce the smaller granule fraction [8]. The *viscosity* of the binder liquid affects the droplet size, and thereby the size of the granule [17]. The *solvent* of the binder solution can be either aqueous or organic, depending on the moisture sensitivity of the material to be granulated. Aqueous solvents are preferred because of explosion hazards and for environmental reason [8].

1.3 Mechanisms which describe growth of granules

In the section above, a number of factors were given which influence the granulation process. Although these factors are helpful to achieve insight in the granulation process and are useful to develop a new process, they are not a mechanistic model of the process.

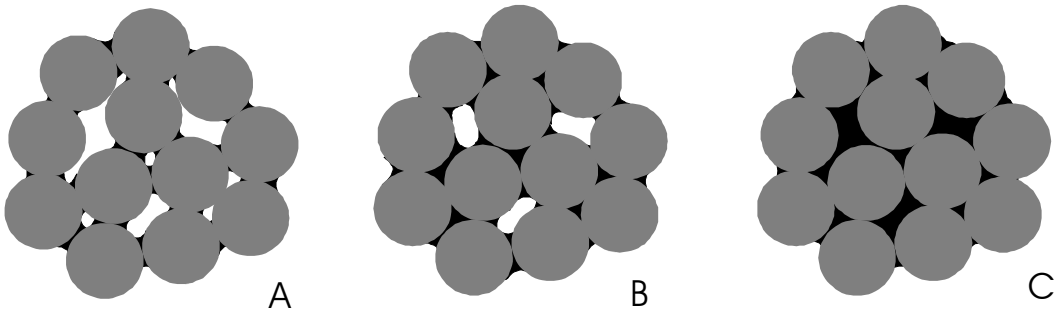

Figure 1.1 Three states of water content for an assembly of spherical particles [32]
a. Pendular state b. Funicular state c. Capillary state

Newitt and Conway-Jones [32] postulated one of the first models used to describe agglomeration. They studied three important stages of a wet granule, depicted in Figure 1.1. The strength of the granules was considered for the rotating drum agglomeration process. They showed that the strength of a granule depends on the liquid saturation. Rump [33, 34] presented a model that can be used to determine the strength of granule in a dry or a wet stage. Schubert extended this research [55].

Maraglou and Nienow [21] proposed a verbal physical model of the agglomeration process in the fluid bed. In this model several important mechanisms are depicted (Figure 1.2). Maraglou and Nienow suggest three possibilities of the growth of granules (Figure 1.2, mechanisms i, j and k). This agglomeration is considered a balance of break-up forces and binding strengths. This seems to contrast with the findings of Scheafer and Worts [31], which indicated that the rupture forces in the fluid bed are of minor consequence. However, Scheafer and Worts used relative large droplets compared to their primary particles, so growth took place by engulfment [28]. However, as granules become larger and all primary particles (initial powder) are agglomerated, the droplet size may be smaller than the granule size and mechanisms i, j or k may occur.

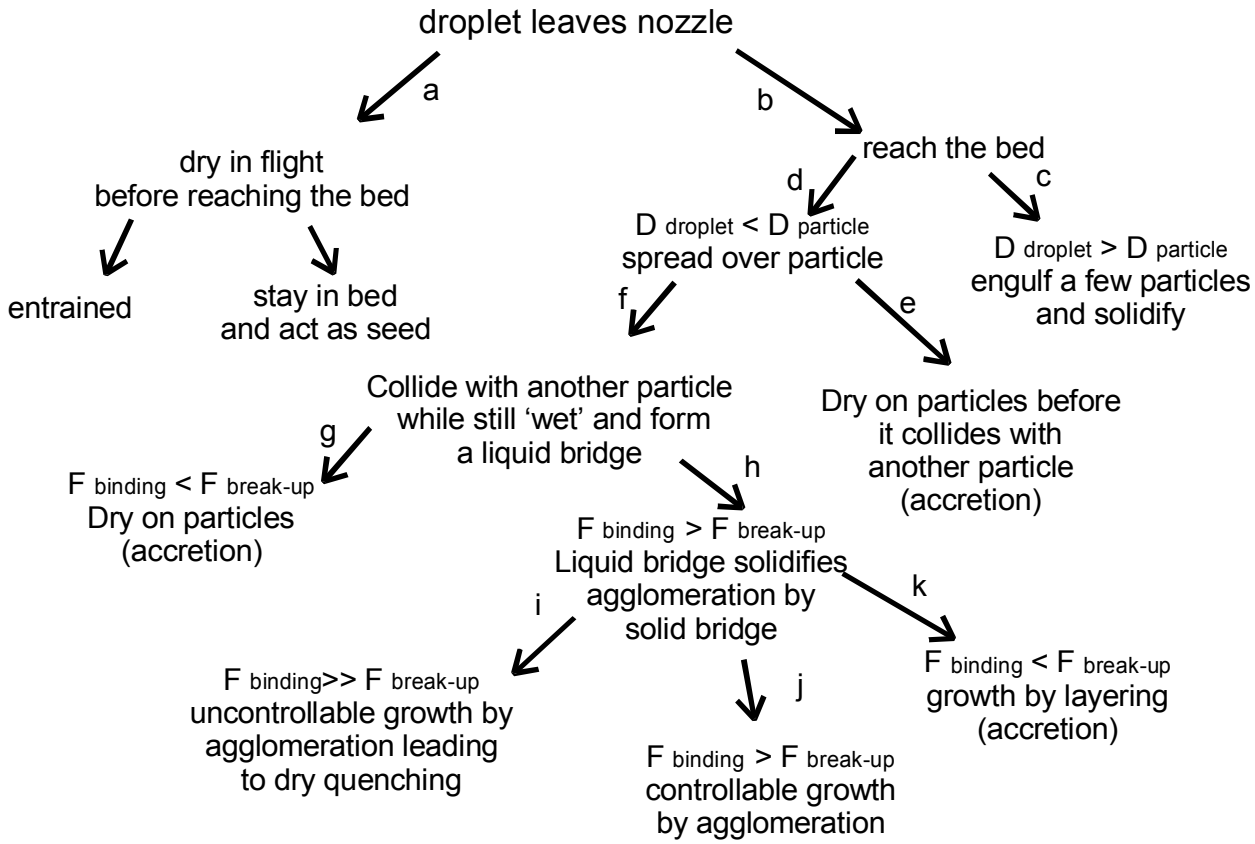

Figure 1.2 Mechanism of growth according to Maraglou and Nienow

Robinson and Waldie [56] showed that 'growth by layering' occurred with top spraying and that the rupture of granules was hardly detectable. Smith and Nienow [20] showed that the growth decreased during agglomeration due to the suction of liquid into the porous structure, which resulted in insufficient liquid at the surface of a granule to bind other granules or particles. Possibly, the growth mechanisms proposed by Maraglou and Nienow [21] depend largely on material properties of the binder liquid.

An attempt to incorporate the material properties on a qualitative and somewhat on a quantitative manner was made by Iveson and Litster [1]. They describe a shear regime, which starts from a stage of no rupture to a stage of server rupture forces. In this way, they covered the whole range from a low-shear to high-shear devices. This is depicted in Figure 1.3.

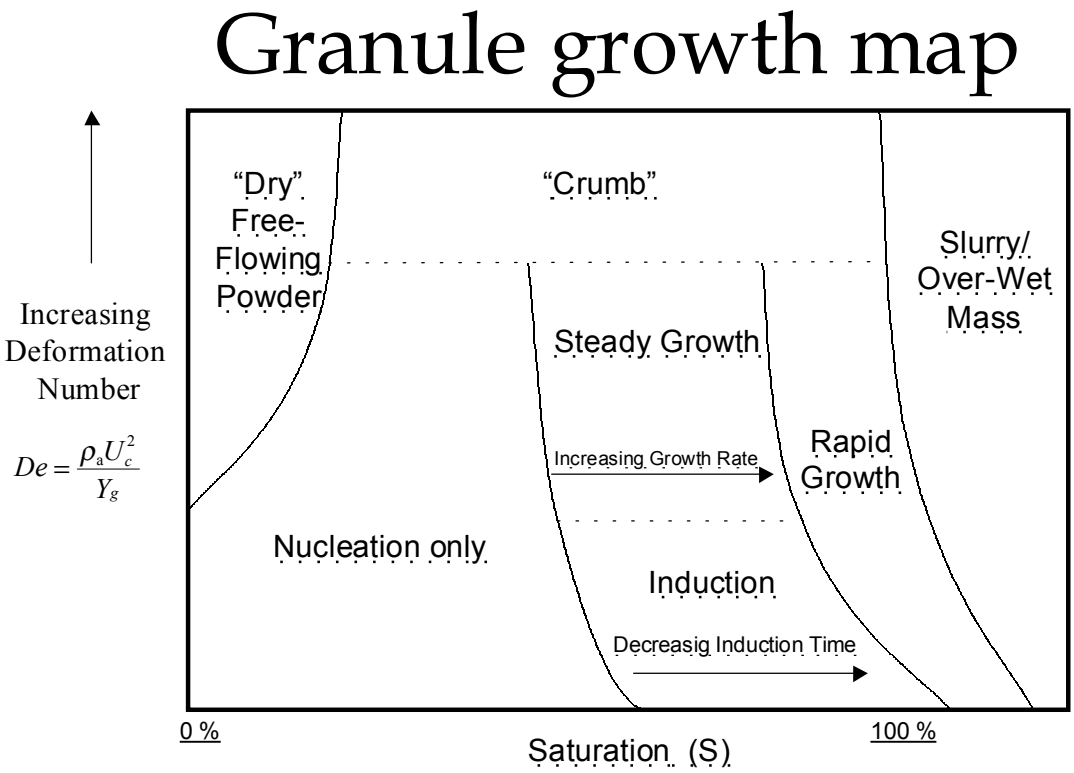

Figure 1.3 Growth regime map [1]

In Figure 1.3 De is the deformation number, ρ_g the granule density, U_c the granule velocity, Y_g the granule dynamic yield stress, and S the pore saturation.
Densification of granules is not an issue in fluid bed agglomeration. From this and the mechanism proposed in Figure 1.3 by Iveson and Litster, we draw the conclusion that growth in the fluid bed is governed by nucleation (engulfment) and layering.

1.4 An introduction into the fundamentals of mixing of particles in a fluidised bed

The powder in the fluid bed determines the fluidisation behaviour. Geldart [57] introduced a classification of four types of fluidisation, depending on particle size and density (Figure 1.4). In the agglomeration process the particles change in size and fluidisation behaviour during the agglomeration period, starting typically as a class C powder or a class A powder, and moving to a class B powder or even a class D powder.

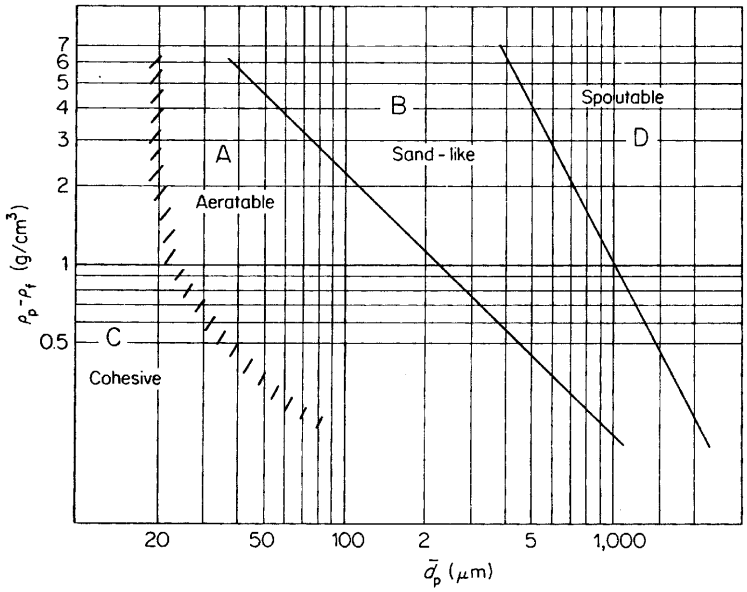

Figure 1.4 Classification of powders for fluidisation according to Geldart [57]

Group A: Easily fluidised powders with particle size between 30 and 150 μm and particle density smaller than 1400 kg/m³. When increasing the gas fluidisation velocity the powder bed has a large expansion.
Group B: Good bubbling fluidisation. The particle diameter of the powder is between 150 and 500 μm and the density is between the 1400 and 4000 kg/m³. Almost no inter-particle forces are encountered for these powders. Only a slight bed expansion occurs while increasing the gas fluidisation velocity.
Group C: Difficult to fluidise. The particle diameter of the powder is smaller than 30 μm. Cohesive powder leads to plug flow and channelling when fluidisation is attempted.
Group D: Difficult to fluidise. The particle diameter is larger than 600 μm or has a very high density. The bed has an irregular spouting behaviour during fluidisation.

The distribution of liquid in the fluid bed is determined by mixing of the wetted particles. The particle mixing in the fluid bed is difficult to characterise. The mixing intensity changes during the agglomeration process due to changed bed humidity and the changed size and density of the fluidised particles. Mixing is an important factor because, it influences wetting of powder in the spray zone and the drying of granules in the bed.
The particle transport in a bubbling fluid bed can be roughly described by an upward transport of material in the wake of a bubble to the top of the bed with a consequent downwards motion in the bulk emulsion [58-61]. These mechanisms are depicted in Figure 1.5 for granules formed at the bed surface using top spraying.

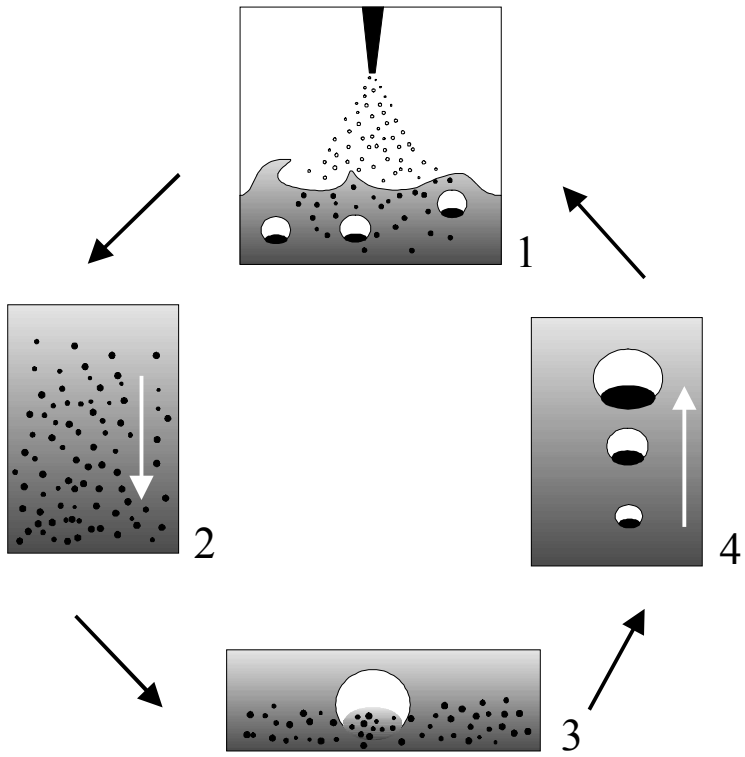

Figure 1.5 Particle transport in a fluidised bed agglomeration process
1. Formation of granules at the bed surface 2. Segregation of granules 3. Bubble and wake formation near the distributor plate 4. Transport of bubble and wake to the bed surface

The bubble volume determines the wake volume and therefore the particle transport. The void/wake ratio decreases with increasing bubble size. A simple relation referred to as the n-type two-phase theory [62, 63] relates the total flow of gas in bubble voids to the minimum fluidisation velocity (U_{mf}):

$$U_e = U_G - U_{mf}\left(1 + nf_b\right) \qquad 1.1$$

Here U_G is the fluidisation velocity, U_{mf} is the minimum fluidisation velocity, f_b is the volume fraction of the bed occupied by bubbles, n is a positive number and U_e is the excess gas velocity. The part of the gas that is not necessary for fluidisation is called the excess gas velocity (U_e). It is approximately equal to the total bubble void volume rising per second per unit cross-section area of the bed. The n is zero in ideal two-phase flow theory. In practice, n varies slightly with U_G, the bed height and the particles used. Therefore, it is a difficult parameter to use when scaling up the process.

During agglomeration, U_{mf} will increase as the granule diameter increases. Consequently the excess gas velocity will decrease and so will the overall bed mixing.
Another aspect that influences the mixing is the humidity in the emulsion phase of the fluid bed. Hartholt [64] found that, when the relative humidity (rH) of a fluidised bed containing glass beads increases above a value of 60%, U_{mf} increases. This is because the adsorption of water molecules on the particle surface will increase at higher relative humidity. The adsorbed liquid layer can enhance the interparticle forces and therefore change the bed voidage at incipient fluidisation severely by formation of liquid bridges between the particles. This starts to become significant with approximately 2 to 3 monolayers of water molecules on the particle surface [65]. A decrease of the interparticle forces with increasing rH is also possible since the enhanced conductivity can decrease electrostatic forces. The influence of rH on the minimum fluidisation velocity depends on the particle size, surface roughness and other material properties such as moisture affinity of the particle surface. The increase in U_{mf} will result in decreased mixing. Eventually, the bed material becomes so cohesive that fluidisation becomes impossible. This results in channel formation and collapse of the fluid bed. The defluidisation depends on the gas velocity as well: the gas velocity can be increased to overcome the larger interparticle forces. Therefore it is necessary to control the relative humidity of the bed, since above a critical value it will influence the mixing behaviour.

The axial distribution of the granules in the bed is also considered important for the process. Particle mixing and segregation in fluidised beds containing a mixture has been studied in several papers [59, 66, 67].

1.5 Scaling down

Much data on the agglomeration process in a full-scale fluid bed such as effects of operating variables, material parameters and agglomerate growth rate curves have been collected in the past. Although this work has contributed to an improved insight of the process, scaling up is still difficult [68-71]. As already mentioned, the description of the growth of granules in fluid bed agglomeration is complicated, because many mechanisms, such as wetting, drying and mixing of the powder and granules are involved. These mechanisms determine the properties of the granule. The mechanisms can be studied in detail for a single granule [28, 72]. When the conditions applied to the single granule resemble the conditions of the full-scale process, one can use these small-scale experiments to describe the full-scale process conditions. This approach, called scaling down, is a good tool to study important aspects of the mechanisms involved. In full-scale fluid bed agglomeration, the wetting of the powder occurs in a large, vigorously moving bed of particles, onto which droplets of different sizes are simultaneously sprayed. Some authors used this approach to study the initial wetting of powder [28, 72, 73]. Large droplets were used to study the granule growth in a low shear environment. These large droplets are one order of magnitude larger than the droplets used in the full-scale agglomeration processes. Furthermore, drying was not taken into account. These experiments do not simulate the full-scale process as a whole, but only the wetting behaviour. Nevertheless, they can give insight in this aspect of the agglomeration process in a fluidised bed.

This thesis discusses the development of a scaling down tool, which proves to be representative for several aspects of the full-scale process.